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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,571	09/29/2004	Hitoshi Kitayama	230991	9555

23460 7590 06/18/2007

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EXAMINER
FETTEROLF, BRANDON J

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
06/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,571	KITAYAMA ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 04/04/2007 in response to the previous Non-Final Office Action (04/04/2007) is acknowledged and has been entered.

Claims 1-5 and 19-25 are currently pending and under consideration.

Information Disclosure Statement

The Information Disclosure Statement's filed on 12/10/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner has considered the information disclosure statements. A signed copy of the IDS is attached hereto.

Rejections Withdrawn:

The rejection of claims 1-18 under 35 U.S.C. 102(b) as being anticipated by Petzold et al. (European Journal of Cardio-thoracic Surgery 2001; 19: 859-864) or Watanabe et al. (Clinical Biochemistry 2001; 34: 257-263, IDS) are withdrawn in view of Applicant's amendments.

Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps is 2) a correlation step describing how the detection of H-FABP in the blood separated from a human relates back to the preamble of the method objectives, e.g., determining toxicity to the heart of an anthracycline-type anticancer agent. For example, it is unclear whether an

increase in H-FABP correlates with toxicity or whether a decrease in H-FABP correlates with toxicity.

In response to this rejection, Applicants assert that claim 1 has been amended to recite particular methods steps, including obtaining a sample from a human to whom has been administered an anthracycline-type anticancer chemotherapeutic agent, measuring the level of human H-FABP protein in the blood sample, comparing the measured level of human H-FABP protein with a standard level of human H-FABP protein, and determining toxicity to heart of the anthracycline-type anticancer chemotherapeutic agent in the human based on the comparison of the measured level of human H-FABP protein with the standard level of H-FABP protein.

These arguments have been carefully considered, but are not found persuasive.

With regards to the amendments, the Examiner acknowledges and appreciates Applicants for amending the claims to include the recited steps. However, the Examiner recognizes that the claims still appear to be unclear with respect to the preamble. As stated above, it is unclear whether an increase in H-FABP correlates with toxicity or whether a decrease in H-FABP correlates with toxicity.

New Objections and/or Rejections necessitated by amendment:

Claim Objections

Claim 22 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 22 further limits claim 1 by reciting that the method further comprises administering the anthracycline-type anticancer chemotherapeutic agent to the human prior to obtaining the blood sample from the human. However, claim 1 already appears to set forth that the anthracycline-type anticancer chemotherapeutic agent was administered to the human prior to obtaining a blood sample, see for example step (a) of claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 and 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 and 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: what the standard level is; and further, if the standard level is the cut-off value, as recited in, for example, claim 21, what the cut off value is. For example, it is unclear whether the cut off value is a predetermined value of H-FABP from a collection of healthy individuals or if the cut-off value is a value obtained from the individual prior to administration of the anthracycline-type anticancer agent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5 and 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carulli et al. (Tumori 1985; 71: 463-468) in view of Okamoto et al. (Clin. Chem. Lab. Med. 2000; 38: 231-238).

Carulli et al. teach a method of determining the concentrations of circulating myoglobin in the serum of a cancer patient after treatment with low doses with adriamycin (page 464, 1st column,

2nd full paragraph). In particular, the reference teaches that significant increases in myoglobin levels were found after injection of low doses of the adriamycin which indicates that the measurement of myoglobin offers an indication of myocardial or skeletal muscle damage caused by myoglobin (page 467, 1st column, last paragraph). For example, the reference teaches the measurement of myoglobin concentration prior to and after adriamycin administration (page 466, Figure 1).

Caullii et al. do not explicitly teach measuring the level of H-FABP protein in the blood sample as a way of determining the toxicity in the human.

Okamoto et al. teach a clinical evaluation of serum H-FABP levels by using a direct sandwhich-ELISA as a diagnostic marker in the early phase of acute myocardial infarction in comparison with myoglobin and creatine kinase isosyme MB. With regards to the sandwich ELISA, the reference teaches that the sandwich ELISA utilizes two anti-human H-FABP MAbs (page 232, 2nd column, 4th full paragraph). Moreover, the reference teaches that serum concentrations of H-FABP in patients with AMI was significantly higher than the levels of the non-AMI group and the normal healthy subjects, wherein the mean concentration of H-FABP were 2.8 ng/mL for healthy, 111 ng/mL for the confirmed AMI and 8.3 ng/Ml for the non-AMI group with chest pain (page 233, 2nd column, 2nd full paragraph and page 234, Figure 2). The reference further teaches that H-FABP is a more sensitive and specific marker than myoglobin and is a good alternative to myoglobin for detecting acute myocardial infarction because myoglobin is abundant in skeletal muscle as well as the myocardium (page 237, 1st column, middle of 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to detect H-FABP in the method taught by Carulli et al. in view of the teachings of Okamoto et al.. One would have been motivated to do so because Okamoto et al. teach that H-FABP is a more sensitive and specific marker than myoglobin and that it is a good alternative to myoglobin for detecting acute myocardial infarction Thus, one of ordinary skill in the art would have a reasonable expectation of success that by detecting H-FABP in humans exposed to doxorubicin, one would achieve a simple and rapid method of determining doxorubicin cardiotoxicity characterized by a higher level of H-FABP in the serum.

Conclusion

Therefore, NO claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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BF

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